REMARKS

Applicant respectfully requests reconsideration and allowance of all pending claims.

I. Status of the Claims

Claims 1-23 remain pending in this application.

II. 35 U.S.C. 103(a) Rejection

For the reasons set forth in detail below, as well as for the reasons set forth in Applicant's previous submissions (including Amendments A, B and C, which in the interests of brevity will not be repeated in full here), Applicant respectfully requests reconsideration of the rejection of claims 1-23 under 35 U.S.C. §103 as being obvious in view of the combination of Midha et al. (U.S. Patent No. 6,127,385) and Epstein et al. (U.S. Patent Publication No. 2002/0103162).

A. The Claimed Subject Matter

As previously noted, the present application is directed to an **oral** methylphenidate solution (e.g., a solution of the free base or a pharmaceutically acceptable salt thereof) that has improved chemical stability, and therefore improved shelf-life or **storage stability** as well. (See, e.g., paragraphs [0001] and [0010].) Applicant has discovered that by preparing an **oral** solution of methylphenidate using a solvent system comprising a combination of water and a non-aqueous solvent, and in particular an aqueous **solvent system** comprising **less than about 50% water** (or alternatively **greater than about 50% of the non-aqueous solvent**), the chemical stability, and therefore the shelf-life or storage stability, of the solution is improved.

B. The Cited Art

Midha et al. disclose a method of treating depression in a patient by oral or non-oral administration of the active 1-threo-methylphenidate, which may be in the form of the free base or a pharmaceutically acceptable salt. Although they make a general reference to a solution containing the active, ascorbic acid, and an aqueous or non-aqueous solvent, they **fail to disclose or suggest** a **storage stable** solution comprising the active in a **solvent system** that in turn comprises both water and a non-aqueous solvent, **wherein the concentration of water therein is less than about 50%.**

Furthermore, it is to be noted that Midha et al. **do not make any specific reference at all** to the concentration of water, or the concentration of the non-aqueous solvent, in a solution that contains both in combination with the active. Applicant respectfully submits this is because Midha et al. are **simply not concerned**

with the storage stability or shelf-life of such a solution. Evidence of this may be found in the fact that they **do not even reference storage stability** or shelf-life as factors to be considered when preparing such a solution. Rather, they are simply interested in the **administration** of their solutions or compositions.

Epstein et al. disclose methods and compositions for enhancing long-term memory function and/or performance. Although they make a general reference to the preparation of a solution of a methylphenidate compound using, among other things, water, a polyol or a mixture thereof as a solvent, like Midha et al., they also fail to disclose or suggest a **storage stable** solution comprising the active in a **solvent system** that in turn comprises both water and a non-aqueous solvent, **wherein the concentration of water therein is less than about 50%.**

Furthermore, it is to be noted that Epstein et al. **do not make any specific reference at all** to the concentration of water, or the concentration of the non-aqueous solvent, in a solution that contains both in combination with the active. Applicant respectfully submits this is because Epstein et al., like Midha et al, are **simply not concerned about the storage stability** or shelf-life of such a solution. Evidence of this may be found in the fact that **they do not even reference storage stability** or shelf-life as factors to be considered when preparing such a solution. Rather, they too are simply interested in the **administration** of their solutions or compositions.

C. (Current) Declaration of Clifford J. Herman

Applicant notes the following statement by the Office on page 3 of the present action (first paragraph):

> [T]there is nothing to show that compositions comprising more than 10-45% of water as presently claimed, would provide a composition that is not storage stable. There is no indication that varying amounts of water or the solvent system would interfere with storage stability . . .

In response thereto, and in further support of the contentions presented herein with respect to the shelf-life or storage stability of the claimed oral solution of methylphenidate, and in particular to the presence of an aqueous solvent system therein comprising less than about 50% water (or alternatively greater than about 50% of the non-aqueous solvent), the Office's attention is called to the Declaration of Applicant and Inventor Clifford J. Herman, which is being filed simultaneously with this Letter.

As stated in Mr. Herman's current Declaration, consistent with Example 1 of the present application, tests were conducted to illustrate the improved stability achieved in a solution comprising methylphenidate, or methylphenidate HCl, and a solvent system that has a water concentration of less than 50%, as compared to similarly prepared solutions that have a water content of greater than 50%. Specifically, solutions were prepared having a methylphenidate concentration of either 1 mg/ml or 2 mg/ml, and a citric acid concentration of 2.5 mg/ml, in a mixed solvent system having a water content of either 35%, 70% or 90%. Samples of these solutions were then stored for a period of 4 weeks at 25°C and 60% relative humidity, or 40°C and 75% relative humidity. Aliquots of

these stored solutions were taken at 2 weeks and 4 weeks, and analyzed for threo-alpha-phenyl-2-piperidine acetic acid (TA), because the primary route of methylphenidate HCl degradation in solution is hydrolysis that results in the formation of TA.

As can been see from the graphical results of these tests, which are provided in Mr. Herman's current Declaration, the solutions prepared in a solvent system having a water content of greater than 50% consistently contained **significantly more** TA, and thus were significantly less stable, than the solutions prepared in a solvent system having a water content of less than 50%. Specifically, the graphs show that the solutions prepared in a solvent system having a water content of 70% contained approximately **three times more** TA after 4 weeks of storage than the solutions prepared in a solvent system having a water content of 35%, while the solutions prepared in a solvent system having a water content of 90% contained approximately **four times more** TA after 4 weeks of storage than the solutions prepared in a solvent system having a water content of 35%.

In addition, tests were conducted to illustrate the improved stability achieved in a solution comprising methylphenidate, or methylphenidate HCl, a solvent system that has a water concentration of less than 50%, and an organic acid within a concentration in the range of about 0.5 mg/ml to about 5.0 mg/ml (as recited in claims 2 and 9), or about 0.5 mg/ml to about 3.0 mg/ml (as recited in claim 14), as compared to a similarly prepared solution that has an organic acid concentration outside the recited range. Specifically, solutions were prepared having a methylphenidate concentration of either 1 mg/ml or 2 mg/ml, a mixed solvent system having a water content of 35%, and a citric acid concentration of either 0.25 mg/ml, 2.5 mg/ml, or 7.5 mg/ml. Samples of these solutions were then stored for a period of 4 weeks at 40°C and 75% relative humidity. Aliquots of these stored solutions were taken after 4 weeks and analyzed for threo-alpha-phenyl-2-piperidine acetic acid (TA). As can been see from the tabulated results of these tests, which are provided in Mr. Herman's current Declaration, the solutions prepared having a citric acid content of either 0.25 mg/ml or 7.5 mg/ml consistently contained between approximately **30% and 60% more** TA, and thus were significantly less stable, than the solutions prepared having a citric acid content of 2.5 mg/ml.

D. (Prior) Declaration of Clifford J. Herman

As noted in Applicant's Letter to the Patent Office dated February 5, 2008, the above-noted interpretations of the Midha et al. and Epstein et al. references are supported by the prior Declaration of Clifford J. Herman (also dated February 5, 2008). In his prior Declaration, Mr. Herman stated that a completely aqueous solvent system (or even a solvent system that includes greater than about 50% water) is not suitable for a methylphenidate solution, due to problems with solubility and storage stability. Mr. Herman also stated he discovered that, in order to preserve the storage stability of the methylphenidate solution, the solution needs to comprise less than about 50% water (or alternatively, greater than about 50% of a non-aqueous solvent). Furthermore, Mr. Herman stated that **both of the cited references failed to recognize or acknowledge** that methylphenidate solutions are inherently unstable, and that none of the solutions or compositions disclosed in the working Examples or described anywhere else therein

comprise less than about 50% water (or alternatively, greater than about 50% of the non-aqueous solvent). As a result, there is no reason to believe that any of the solutions prepared in the cited references are storage stable.

Additionally, with regard to dependent claim 2, as well as independent claims 9 and 14, Mr. Herman stated that **the cited references also failed to recognize** the benefit of including the recited concentrations of an organic acid in the methylphenidate solution, in order to further stabilize the solution. Specifically, as noted in the prior Declaration of Mr. Herman, the addition of an organic acid (e.g., citric acid) to the methylphenidate solution at the recited concentration (e.g., a concentration of from about 0.5 mg/ml to about 5.0 mg/ml) enables better control of the pH of the methylphenidate solution, which further stabilizes the solution. While Epstein et al. list citric acid as a metal chelating agent (see, e.g., U.S. Patent Application Publication No. 2002/0103162 at paragraph [0274]), there is no suggestion in this reference of using citric acid, or any other organic acid, as a stabilizing agent. Furthermore, there is no suggestion to use an organic acid in the amounts recited in Applicant's claims 2, 9 and 14.

E. The Claimed Subject Matter is Not Obvious

Applicant respectfully submits the Office has failed to establish a *prima facie* case of obviousness, because (i) each and every element of the claims has not been disclosed or suggested, and/or (ii) motivation is simply not provided to prepare the claimed storage stable methylphenidate solution. Applicant submits that Midha et al. and Epstein et al., both alone and in combination, fail to disclose or suggest a storage stable solution designed for **oral** administration comprising, among other things, methylphenidate, or methylphenidate HCl, and an aqueous solvent system that has a water concentration of less than 50%. More specifically, the combination of Midha et al. and Epstein et al. fail to disclose an **oral, storage stable solution** comprising such an aqueous solvent system, wherein:

(i) the water concentration is between about 10% and about 45% and the non-aqueous solvent concentration is at least about 50% (Claim 1);

(ii) the water concentration is less than about 50%, the polyol concentration is between about 30% and about 70%, and the glycol concentration is between about 10% and about 70% (Claim 9);

(iii) the water concentration is between about 10% and about 45%, the polyol concentration is between about 40% and about 60%, and the glycol concentration is between about 10% and about 30% (Claim 14); or,

(iv) the water concentration is between about 30% and about 40%, the polyol concentration is between about 45% and about 55%, and the glycol concentration is between about 10% and about 20% (Claim 19).

Notably, both Midha et al. and Epstein et al. **fail to disclose or suggest any specific details** relating to an **oral, storage stable solution** comprising methylphenidate as the active in combination with water and another non-

aqueous solvent; that is, neither reference provides details of the water content or the non-aqueous solvent content in a solution **designed for oral administration**.

Applicant also submits that there is simply **no reason or motivation** for one of ordinary skill in the art to modify the disclosures of Midha et al. and Epstein et al. in order to prepare a storage stable solution **designed for oral administration** comprising a solvent system as recited in any one of claims 1, 9, 14 or 19, because **neither Midha et al. nor Epstein et al. provide any link between the solutions they generally reference and the storage stability or shelf-life thereof.** In fact, as previously noted above, they do not even identify storage stability or shelf-life as a factor to be considered when preparing a solution designed for oral administration.

Applicant notes the Office again asserts that:

> it is obvious to vary and/or optimize the amounts . . . of aqueous and non-aqueous solvents . . . **according to the guidance provided** by Midha et al. and Epstein et al. to provide a composition having the desired properties such as the desired concentrations and percentages of each component to formulate an effective methylphenidate solution **for administration**. (See the Office action at the bottom of page 4. Emphasis added.)

However, Applicant respectfully submits that providing guidance for preparation of a solution of methylphenidate for "administration" is not the issue here. Rather, the issue is providing **motivation** to prepare a solution **designed for oral administration** that has improved storage stability and shelf-life, and thus has the composition as claimed. As noted in MPEP §2144.05(II)(B), **a particular parameter must first be recognized as a result-effective variable** before the determination of the optimum or workable ranges of the parameter might be characterized as routine experimentation. (Citing *In re Antonie*, 195 USPQ 6 (CCPA 1977).) Notably, **neither Midha et al. nor Epstein et al. make such a recognition.** More specifically, nowhere in either reference is the storage stability and shelf-life of an oral methylphenidate solution linked to the water content of the solvent used therein, or for that matter even mentioned.

Furthermore, as noted in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, the Federal Circuit has stated that "in cases involving new chemical compounds, **it remains necessary to identify some reason that would have led a chemist to modify** a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound."[1] The same is true here with respect to the claimed solution and the solvent system used therein. Therefore, the Office has provided no more than an "obvious to try" reason; specifically, that the compositions of Midha et al. and Epstein et al. would be modified to have "the desired properties such as the desired concentrations and percentages of each component to formulate an effective methylphenidate solution for

[1] 492 F.3d 1350, 1357 (Fed. Cir. 2007). (Emphasis Added.)

administration." (See the final Office action at page 4.) Nowhere, however, is a reason specifically articulated as to why one skilled in the art would modify the **amount of water and/or non-aqueous solvent** to produce the desired **storage stable** solution for **oral** administration. As such, Applicant respectfully submits Midha et al. and Epstein et al. fail to provide a reason or the guidance, and therefore the motivation, to prepare an oral, storage stable solution having the concentrations of aqueous and non-aqueous solvents in the ranges as required in any one of Applicant's claims 1, 9, 14 or 19.

In view of the foregoing, Applicant respectfully submits that the Office has failed to meet its burden in establishing a *prima facie* case of obviousness here, because each and every element of the claimed storage stable solution has not been disclosed or suggested by the combination of Midha et al. and Epstein et al., and/or because motivation is simply not provided by the combination of Midha et al. and Epstein et al. to prepare a storage stable solution as claimed. Therefore, reconsideration of the rejection of claim 1-23 is respectfully requested.

CONCLUSION

In view of the foregoing, Applicant respectfully requests favorable reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge Deposit Account 13-1160 for any fees due for the submission of this Letter, including a three (3) month extension of time for responding to the present Office action, as well as the Declaration and/or Request for Continued Examination being filed simultaneously herewith.

Respectfully submitted,

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